

# Epidemiology and risk factors of renal cell carcinoma: literature review and correlation according to Lithuanian people epidemiological risk factors

## Inkstų vėžio epidemiologija ir rizikos veiksniai: literatūros apžvalga ir epidemiologinių rizikos veiksnių koreliacija Lietuvos gyventojų populiacijoje

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### Background

Renal cell carcinoma (RCC) is one of the most dangerous urological cancers. Several risk factors for RCC have been identified, including smoking, obesity, and hypertension. Other risk factors for RCC could be dietary practices (alcohol consumption, food), physical activity, occupational exposures, drugs, other diseases, reproductive and hormonal factors, and others.

### Results

Our literature analysis revealed a high smoking incidence in the past and the present decrease in smoking by 50%. If smoking is a strong causal factor of RCC, in the nearest future, in 10–20 years, we will have a decrease in RCC incidence. In Lithuania, over the last ten years, the prevalence of overweight and obesity among men has increased, and in women it has decreased. The significant reduction in obesity, therefore, would dramatically decrease the incidence of those cancers and lower the mortality rate of RCC in Lithuania. The high prevalence of hypertension and the still low awareness among hypertensive men and women could also be a cause of high incidence of RCC in Lithuania. The Lithuanian population eats many fatty and high-protein foods. Meat is seen almost in everyday meal, and another unfavorable factor is the low consumption of vegetables, which could be a preventive meal. This problem is seen even in school-age children.

## Conclusion

In the analysis of risk factors and their contribution to the high incidence of RCC in the Lithuanian population, we have found that the main risk factor of RCC is highly frequent in population and could be the main reason of high RCC incidence.

**Key words:** renal cell carcinoma, risk factors, obesity, smoking, arterial hypertension

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## Įvadas

Viena agresyviausių vėžio rūšių urologijoje yra inkstų ląstelių vėžys. Pagrindiniai inkstų vėžio rizikos veiksniai yra rūkymas, nutukimas ir padidėjęs kraujo spaudimas. Kiti rizikos veiksniai galėtų būti mitybos įpročiai (alkoholio vartojimas, maisto produktai), fizinis aktyvumas, žalingi darbo veiksniai, vaistai, ligos, reprodukciniai ir hormoniniai veiksniai.

## Rezultatai

Atliekant literatūros apžvalgą, nustatytas didelis rūkymo dažnis praeityje ir 50 proc. mažėjantis rūkymo dažnis dabar. Jei rūkymas yra svarbus inkstų vėžio rizikos veiksnys, netolimoje ateityje, maždaug po 10–20 metų, sergamumas inkstų vėžiu turėtų sumažėti. Lietuvoje per pastaruosius 10 metų atsvaris ir nutukimas vis dažniau nustatomas vyrams, tačiau moterims jis mažėja. Reikšmingas nutukimo sumažinimas populiacijoje leistų gerokai sumažinti sergamumą ir mirštamumą nuo inkstų vėžio. Didelis sergamumas padidėjusiu kraujo spaudimu ir menkas vyrų ir moterų supratingumo lygis taip pat galėtų būti didelio sergamumo inkstų vėžiu priežastis. Lietuvoje gyventojai valgo daug riebalų ir baltymų turinčio maisto. Mėsa yra kasdienio raciono dalis, o kitas nepalankus veiksnys yra per mažas daržovių vartojimas. Ši problema itin aktuali jau mokyklinio amžiaus vaikams.

## Išvados

Analizuojant rizikos veiksnis ir jų įtaką dideliame Lietuvos populiacijos sergamumui inkstų vėžiu, nustatyta, kad rizikos veiksniai yra labai paplitę ir tai gali būti pagrindinė didelio sergamumo priežastis.

**Reikšminiai žodžiai:** inkstų vėžys, rizikos veiksniai, nutukimas, rūkymas, padidėjęs arterinis kraujo spaudimas

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## Introduction

Renal cell carcinoma (RCC) is one of the most dangerous urological cancers. It is a widely known fact that the best treatment modality for RCC is nephrectomy or nephron sparing surgery (NSS). RCC treatment involves tumor removal, and if no metastases are seen, this surgical movement cures the patient. RCC is dangerous because it gives no signs of the disease until it is too late. In more than 50% RCCs are detected incidentally when a non-invasive imaging is used to investigate a variety of nonspecific symptoms [1–3]. In Lithuania, the main cause of incidental diagnoses of RCC is primary arterial hypertension, because due to the high blood pressure ultrasound is performed and renal tumor diagnosed.

Kidney cancer is the ninth most common cancer in developed countries and the eighth in Lithuania [4–6]. The highest incidence of kidney cancer is observed in the Czech Republic, with the rates of approximately 22 per 100 000 in men and 11 per 100 000 in women. High rates are also observed in Estonia, Hungary, Slovakia, Lithuania, Latvia, and Germany and among some Afro-American populations of the USA [7]. The cause of the high incidence and mortality rates in Lithuania is not

clear. The Westernization of the Lithuanian population could be a cause.

Several risk factors for RCC have been identified, including smoking, obesity, and hypertension [3]. Other risk factors for RCC could be dietary practices (alcohol consumption, food, etc.), physical activity, occupational exposures [8], drugs, other diseases, reproductive and hormonal factors [9], and others.

## Situation in Lithuania

According to the GLOBOCAN 2012 project information, the incidence of RCC is 13.2 cases per 100 000 people in the Lithuanian population, and it is the second country in the world after the Czech Republic, but the mortality rate from RCC in Lithuania is 4.9 cases per 100 000 people, and this is the highest mortality rate in the world [6].

Malignant tumors of the kidney (apart from renal pelvis) account for about 4.5% of all malignant tumors in Lithuania. If we look at the incidence of RCC in the men age group of 30–54 years, we would find that RCC accounts for 9% of young men cancer malignant cancers, and it is the 3rd most common cancer in this

age group. The incidence rate in Lithuanian men is 27.2 per 100 000 men in 2010 and the mortality rate 9.8 per 100 000 men [6]. According to the Lithuanian cancer registry information, the incidence of RCC is still growing. Every year in Lithuania there are newly diagnosed more and more clinical stage I RCC (pT1), however, there is still a very high rate of the diagnosed clinical stage IV (metastatic) RCC. In 2011, the metastatic RCC accounted for 21.3% in male and 13.6% in female [6]. If we have such a high incidence and mortality rates of RCC in the Lithuanian population, the proposal of RCC screening for the risk group people could be considered.

## **Risk factors**

### ***Smoking***

Cigarette smoking is considered a causal risk factor for renal cell cancer by the International Agency for Research on Cancer (IARC) and the U.S. Surgeon General, although the risk associated with cigarette smoking is relatively modest. Compared to never smokers, risk increased about 50% in male and 20% in female smokers [9, 10, 11, 12]. Both current and former smokers have an increased risk of developing RCC, with heavy smokers having the highest incidence [12, 13].

A meta-analysis of data from 19 case-control studies (8,032 cases and 13,800 controls) and five cohort studies (1,457,754 participants with 1,326 renal cell cancer cases) reports statistically significant relative risks of 1.5 and 1.2 for male and female smokers, respectively. There was a strong dose-dependent increase in risk, up to 2- and 1.6-fold among heavy (21 or more cigarettes per day) men and women smokers, respectively [12, 14].

A clear dose-response pattern of risk was apparent, with risk doubling among men and increasing by 58% among women who smoked more than a pack of cigarettes per day [9]. Lubin et al. estimated that smoking fewer cigarettes per day for a longer period of time posted a greater renal cell cancer risk than smoking at a higher intensity for a shorter duration [15]. A meta-analysis of 24 studies showed that compared to lifetime never smokers, ever smoking increased renal cell cancer risk by 54% among men and 22% among women [8, 13].

Cigarette smoking is hypothesized to increase renal cell cancer risk through chronic tissue hypoxia due to carbon monoxide exposure and smoking-related conditions such as the chronic obstructive pulmonary disease. In addition, renal cell cancer patients were shown to have a higher level of DNA damage in their peripheral blood lymphocytes induced by a tobacco-specific N-nitrosamine compared to control subjects. Deletions in chromosome 3p, a frequent site of genetic alterations in renal cell cancer, were also shown to be more common in cultured peripheral blood lymphocyte cells from renal cell cancer patients than control subjects after being treated with benzo[ $\alpha$ ]pyrene diol epoxide, a major constituent of cigarette smoke [9, 16, 17, 18].

According to WHO, trends in both developed and developing countries show that male and female smoking rates have reached the peak and, slowly but surely, are declining. However, the consumption of cigarettes is still growing in the developing countries [19].

According to the newest analysis, in Lithuania one third of the 15–64 year population is smoking (40.5% of male and 23.5% of female). Smoking incidence was growing, but at present it is falling down, and now we have information that from the 21st century to nowadays smoking people decreased by 50% [20]. If smoking is a strong causal factor of RCC, in the nearest future, in 10–20 years, we will have a decrease in RCC incidence.

### ***Obesity***

Obesity is a new civilization disease and a great risk factor for many other diseases that kills young people. Chronic conditions are associated with obesity which makes people disabled. Family members have a lower quality of life due to an obese relative. Chronic conditions are the leading cause of mortality and morbidity and contribute significantly to the overall health expenditures from both a societal perspective as well as an individual one [22].

Among obese people, a statistically significant increased risk was observed for the following 8 cancers: colon, endometrial, esophageal, gallbladder, leukemia, pancreatic, postmenopausal breast, and renal [22].

Excess body weight has been estimated to account for over 40% of renal cell cancers in the United States and over 30% in Europe [8, 9, 21].

A meta-analysis of data from prospective observational studies has estimated that the risk of RCC increases by 24% for men and 34% for women for every 5 kg/m<sup>2</sup> increase in body mass index (BMI) [8, 23].

An independent effect of weight gain has been recently confirmed in a large cohort of U.S. men and women. This study further demonstrated that the increased risk was mostly associated with weight gain during early adulthood, whereas weight gain after midlife was unrelated to risk [8, 24].

The obesity has increased by 10–40% in the majority of the European countries over the last decade [25], the same has happened with the RCC incidence. Another condition that is associated with obesity and with RCC is diabetes mellitus because of increased bioavailable insulin-like growth factor-I (IGF-I) levels that may be one mechanism through which obesity increases the kidney cancer risk [26].

In Lithuania, over the last ten years, the prevalence of overweight / obesity among men has increased from 47% / 10.6% to 52.5% / 14.2%. Opposite trends were found in women: the proportion of overweight women decreased from 51.2% to 46.2% and the proportion of obese from 18.9% to 16.9%. The largest increase in the prevalence of overweight and obesity was observed among men with university education, whereas the decreasing trends were found among highly educated women. In cities, the prevalence of overweight increased among men and reduced among women [27]. One of the many possibilities of a high incidence of RCC may be increased obesity in the Lithuanian population.

In 2006, the Lithuanian High Cardiovascular Risk Programme analyzed middle-aged subjects and found that abdominal obesity and metabolic syndrome were present in 45.4% and 43.8% of cases, respectively [28].

### **Hypertension**

Another well-known risk factor is hypertension. The increase in RCC incidence all over the world, and also in Lithuania, may be associated with the increasing prevalence of hypertension. Most studies have reported risks for renal cell cancer associated with either recorded blood pressure or reported hypertension ranging between 1.2 and 2 or greater [29–31].

Compared to individuals with normal blood pressure, those with the highest blood pressure ( $\geq 100$  mmHg diastolic pressure or  $\geq 160$  mmHg systolic pressure) were found to have twofold or higher risks [8]. In a cohort of Swedish men with sequential blood pressure measurements during follow-up, the risk further increased among those whose blood pressure increased above the baseline level and reduced among those whose blood pressure declined over time [29]. These data suggest that hypertension is a promoting factor in renal cell cancer development, and the risk can be modified with a better control of blood pressure [8]. Chow and colleagues have found that a decrease in diastolic blood pressure during the period of time reduced the risk by 40% in those whose diastolic pressure decreased by more than 14 mmHg (relative risk, 0.6; 95 percent confidence interval, 0.3 to 1.3) and in those whose diastolic pressure decreased by more than 9% (relative risk, 0.6; 95 percent confidence interval, 0.3 to 0.9) [29]. Also, it is clear that the risk of renal-cell cancer in men with a diastolic pressure of 90 mm Hg or more was more than double the risk in men with a diastolic pressure below 70 mmHg [29].

It is still unknown how the elevated blood pressure causes RCC, but it is explained that lipid peroxidation and the formation of reactive oxygen species are found to be elevated in hypertensive individuals and are hypothesized to play a role in renal cell cancer development [32]. The chronic renal hypoxia accompanying hypertension has also been hypothesized to increase the renal cell cancer risk through the up-regulation of hypoxia-inducible factors, which may be a key mediator of kidney oncogenesis [8, 16, 33–35]. The hypoxia-associated hypertension has been shown to increase proximal tubular cell proliferation and glomerular hypertrophy in animal models [8].

A study performed by cardiologists in Lithuania, where they analyzed the condition of men aged 40–54 years and of women aged 50–64 years according to high risk patients of having cardiovascular mortality, and they found that 60.2% had arterial hypertension, 10.3% had diabetes mellitus, 21.5% were current smokers, and 43.8% had the metabolic syndrome. In this study, they also found a very high prevalence of dyslipidemia (88.8%). The prevalence of insufficient physical activity in the whole sample was 50.2% (95% CI: 49.5–51.0%) [28].

Reklaitiene et al. analyzed in their study men and women during 1983–2002 periods and found that hypertension prevalence was 52.1–58.7% and did not significantly change, whereas in women it decreased from 61.0 to 51.0%. There was a significant increase in hypertension awareness among hypertensive men and women (45.0 to 64.4% and 47.7 to 72.3%, respectively) and in treated hypertensives (55.4 to 68.3% in men and 65.6 to 86.2% in women) [36].

The high prevalence of hypertension and still a low awareness among hypertensive men and women could also be a cause of the high incidence of RCC in Lithuania.

### ***Food and drinks***

Another risk factor could be all sorts of beverages and food. A combination of them could be described as a life style in properties. Washio et al. performed a large population-based cohort study in Japan and stated that the increasing incidence of renal cell cancer in the Japanese population may be partly due to the lifestyle westernization. They suggested five risk factors (hypertension, diabetes mellitus, kidney diseases, fondness for fatty food and black tea) and one preventive factor (starchy roots such as taro, sweet potato, and potato) in the Japanese population. In Japan, however, drinking black tea may be a surrogate for westernized dietary habits, while eating starchy roots may be a surrogate for traditional Japanese dietary habits [37].

In most literature talking about beverages, the main factor that is the first to think about is alcohol. In the analysis of 12 prospective studies, renal cell cancer risk decreased with increasing alcohol consumption, with a significant 28% reduction in the risk among those who drank  $\geq 15$  g/day, equivalent to slightly more than one alcoholic drink per day [8]. In contrast, total fluid intake from all beverages, including coffee, tea, milk, juice, soda, and water, has not been consistently linked to the risk. A potential mechanism by which a moderate consumption of alcohol may reduce the renal cell cancer risk is through improvement in insulin sensitivity [38–39], thus lowering the risk of type 2 diabetes, production of insulin-like growth factor-I, and the subsequent risk of renal cell cancer [8].

Other drinks also could be a risk factor, and literature shows that an increased risk among tea drinkers has been

reported in a few studies of renal cell cancer, particularly among women. In spite of the fact that some teas have been found to be mutagenic and contain tannins that appear carcinogenic in laboratory animals, the etiologic significance of these findings is not clear [7]. In Washio et al. study, those who drink black tea (3+ cups/day vs. none: age- and sex-adjusted HR = 13.60, 95% CI: 1.83 to 101.30) have an increased risk of renal cell cancer death even after adjusting for other factors. In addition, those who drink coffee (3+ cups/day vs. none: age- and sex-adjusted HR = 2.69, 95% CI: 0.89 to 8.10) have a marginally increased risk while there is no meaningful association between renal cell cancer death and green tea consumption in the Japanese population [37].

High protein consumption from meat and dairy products has been associated with chronic renal conditions that may predispose to kidney cancer and with an increased risk of kidney cancer, although the evidence is inconsistent [7]. An elevated renal cell cancer occurrence also has been reported among patients with the end stage renal disease awaiting renal transplant, as well as among renal transplant patients [8]. The increased incidence of renal cell cancer has been observed among patients with uremia undergoing hemodialysis, particularly among patients on long-term dialysis and those with the acquired cystic kidney disease [8].

Hsu et al. concluded that cruciferous vegetables were inversely associated with kidney. High levels of cabbage consumption were inversely associated with kidney cancer [40]. However, broccoli and brussels sprouts consumption was particularly low in the population analyzed by Hsu et al., with more than half of the population having never consumed these vegetables, which may explain the lack of association for these items [40].

The Lithuanian population is linked to a higher alcohol consumption, especially beer and vodka type drinks. If we talk about other drinks, as Washio et al. noticed, the same westernization process is seen in Lithuania. Social questioning through the internet in Lithuania showed that about 20% of all tea that the Lithuanian population drink is black tea.

The Lithuanian population loves eating fatty and high-protein foods. Meat is seen almost in everyday meal, and another unfavorable factor is the low consumption of vegetables, which could be a preventive meal.

Zaborskis et al. have found that in Lithuania school-aged children have low intakes of fruits and vegetables. Only 21.1% of boys and 27.1% of girls reported daily fruit consumption. Similarly, 24.9% of boys and 29.6% of girls disclosed vegetable intake at least once daily. Comparing 2010 to 2002, the proportion of girls who consumed fruits daily increased from 24.2% to 31.0% ( $p < 0.001$ ) but the proportion of boys who consumed vegetables daily decreased from 29.3% to 23.1% ( $p < 0.001$ ). In 2006, for both sexes, there was observed an increase in regular (at least five days a week) intake of sweets and chocolates, biscuits and pastries, and soft drinks [41].

### ***Medications and other risk factors***

In all population, as people become older they use more drugs. The thiazide and phenacetin intakes can be considered as risk markers for RCC [7, 9, 42]. Diuretic use has been associated with a five-fold increase in the risk of renal cell cancer among women [7]. A large-scale study in Minnesota observed no relation with regular use or duration of use for aspirin, acetaminophen or even phenacetin. But in Denmark, women that were heavy users of phenacetin had a significant five-fold increase in the risk of renal cell cancer [7]. The use of statins, a class of commonly prescribed cholesterol-lowering agents, has recently been associated with a reduced risk of renal cell carcinoma in a large case-control study nested within a large database of the U.S. veterans. Statins have been shown to inhibit renal cancer cell growth *in vitro* and decrease the amount of pulmonary metastases in animals administered an oral dose of statins. Although statin use has been associated with reduced mortality rates and cancer risk in cohort studies, the specific link to a reduced risk of renal cell cancer has yet to be confirmed in further epidemiologic investigations [8].

Other chemicals that could be seen in everyday life are arsenic, nitrate, and radon in drinking water, which also have not been established as risk factors [9]. An extensive meta-analysis of occupational cohort studies of asbestos-exposed workers showed a little relation to an increased risk for renal cancer [5]. In the early 1980s, unleaded gasoline was suspected as a risk factor for renal cell cancer based on long-term rodent bioassays in which male rats developed renal tumors [5].

Some professions also could be risk factors. For example, mortality studies have suggested that laundry and dry cleaning workers may be at an increased risk for kidney cancer [9]. Fire-fighters and glass-workers were other occupational categories at a higher risk of RCC [42].

And the final factor that can help us prevent renal cancer is physical activity. Physical activity could be a preventive factor not only for renal cancer, but also for many other oncological and non-oncological conditions. Chow et al. state that physical activity may decrease renal cell cancer risk through a number of related pathways, including lowering body weight and blood pressure, improving insulin sensitivity, and reducing chronic inflammation and oxidative stress [8]. Behrens et al. performed a meta-analysis and revealed a statistically significant 12% reduction in the renal cancer risk associated with a high vs. low level of physical activity [43]. Physical activity may prevent the development of renal cancer, partly because it helps reduce obesity, blood pressure, and insulin resistance. Physical activity may also independently decrease renal cancer risk by lowering lipid peroxidation levels. A high level of physical activity has been shown to reduce adiposity, hypertension, insulin resistance, circulating levels of the insulin-like growth factor 1, and lipid peroxidation – factors positively associated with the development of renal carcinoma [43].

In Lithuania, as I have mentioned before, of high incidence is arterial hypertension, so the use of drugs is high and the physical activity is low. These factors also could be among the reasons for the high incidence and mortality rates in the Lithuanian population.

Data by Pomerleu et al. from three national surveys of adults conducted in Estonia, Latvia, and Lithuania in 1997 showed that one in three Estonians and one in five Latvians and Lithuanians had a low physical activity level at work. Half of the respondents (Lithuania: 60%, Latvia: 52%, Estonia: 43%) participated only in sedentary activities during their leisure time. Leisure-time sedentarity was inversely related with the education level in men and women and with income in men. It was also associated with the smoking in men and with inadequate vegetable intake in men and women [44].

## Conclusion

In the analysis of risk factors and their contribution to the high incidence of RCC in Lithuanian population, we have found that the main risk factor of RCC is highly present in the population and could be the main reason for the high RCC incidence.

To conclude, smoking, obesity, hypertension, dietary

habits, drugs, and low physical activity are the main factors that give to Lithuania the high incidence and mortality rate of RCC. These risk factors could be a key in trying to prevent the growth of this incidence. The main idea that could help in treating these patients early and prevent high-stage disease is the screening of risk factor patients' group.

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